FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
204395US0XPCT	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	
09/786370	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/JP99/04905	09 SEPTEMBER 1999
PRIORITY DATE CLAIMED	
05 OCTOBER 1998	

TITLE OF INVENTION
TAPE MATERIAL FOR TRANSCUTANEOUS ABSORPTION

APPLICANT(S) FOR DO/EO/US
Yukino OWAKI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Notice of Priority
PCT/IB/304
PCT/IB/308
Drawings (3 sheets)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/786370	PCT/IB99/04905	204395US0XPCT

21. The following fees are submitted:.	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	10 - 20 =	0	x $18.00	**$0.00**
Independent claims	2 - 3 =	0	x $80.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
TOTAL OF ABOVE CALCULATIONS			=	**$860.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☐	**$0.00**
SUBTOTAL			=	**$860.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**
TOTAL NATIONAL FEE			=	**$860.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**
TOTAL FEES ENCLOSED			=	**$860.00**
				Amount to be: refunded $
				charged $

☒ A check in the amount of **$860.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

22850

WILLIAM E. BEAUMONT
REGISTRATION NUMBER 30,996

SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

March 15, 2001
DATE

204395US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

YUKINO OWAKI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW US PCT APPLN. :
(Based on PCT/JP99/04905)

FILED: HEREWITH :

FOR: TAPE MATERIAL FOR :
TRANSCUTANEOUS ABSORPTION

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown on the attached marked-up copy. A copy of the amended claims in clean form follows:

--3. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1 which causes stratum corneum abrasion only to be a slight extent even when applied continuously for a long period of time.

4. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1 which is excellent in duration of effect on alleviating pains due to herpes zoster or postherpetic neuralgia.

5. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1 which is excellent in duration of effect on alleviating pains on the occasion of high frequency therapy or laser therapy, pains upon treatment of liver spots or dark red birthmarks, pains upon biopsy, pains on the occasion of skin grafting for the treatment of thermal burns, or pains on the occasion of treatment of molluscum contagiosum.

6. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1, wherein the local anesthetic is selected from the group consisting of lidocaine, procaine, oxyprocaine, dibucaine, tetracaine, bupivacaine, mepivacaine, propitocaine, and salts thereof.

7. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1, wherein the local anesthetic is lidocaine.--

Please add the following claim:

--10. (New) A tape preparation for transdermal absorption as claimed in Claim 1 which causes stratum corneum abrasion only to a slight extent even when applied continuously for a long period of time, and is excellent in duration of effect on alleviating pains due to herpes zoster or postherpetic neuralgia.--

REMARKS

Claims 1-10 are active in the present application. The claims are amended to remove multiple dependencies. Claim 10 is supported by the application as filed herewith. No new matter is believed to have been added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

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Marked-Up Copy
Serial No:
Amendment Filed on:

IN THE CLAIMS

Please amend the claims as follows:

--3. (Amended) A tape preparation for transdermal absorption as claimed in Claim 1 [or 2] which causes stratum corneum abrasion only to be a slight extent even when applied continuously for a long period of time.

4. (Amended) A tape preparation for transdermal absorption as claimed in [any of Claims 1 to 3] Claim 1 which is excellent in duration of effect on alleviating pains due to herpes zoster or postherpetic neuralgia.

5. (Amended) A tape preparation for transdermal absorption as claimed in [any of Claims 1 to 3] Claim 1 which is excellent in duration of effect on alleviating pains on the occasion of high frequency therapy or laser therapy, pains upon treatment of liver spots or dark red birthmarks, pains upon biopsy, pains on the occasion of skin grafting for the treatment of thermal burns, or pains on the occasion of treatment of molluscum contagiosum.

6. (Amended) A tape preparation for transdermal absorption as claimed in [any of Claims 1 to 5] Claim 1, wherein the local anesthetic is selected from the group consisting of lidocaine, procaine, oxyprocaine, dibucaine, tetracaine, bupivacaine, mepivacaine, propitocaine, and salts thereof.

7. (Amended) A tape preparation for transdermal absorption as claimed in [any of Claims 1 to 5] Claim 1, wherein the local anesthetic is lidocaine.--

09/786370
JC03 Rec'd PCT/PTO 15 MAR 2001

DESCRIPTION

TAPE MATERIAL FOR TRANSCUTANEOUS ABSORPTION

TECHNICAL FIELD

The present invention relates to a tape preparation for transdermal absorption suited for causing a local anesthetic to be sustainedly absorbed percutaneously and, more particularly, to a tape preparation for transdermal absorption which can cause a local anesthetic, such as lidocaine, to be absorbed through the skin stably and over a long period of time and can be used for alleviating the pain resulting from herpes zoster (hereinafter referred to HZ for short) or postherpetic neuralgia (hereinafter referred to PHN for short), for instance.

BACKGROUND ART

HZ is a disease caused by varicella-zoster virus (hereinafter referred to as VZV for short). About 95% of people experience primary infection with VZV in their childhood and acquire life-long immunity after cure. However, VZV itself, after the infection, is carried latent in sensory ganglions all over the body. While most people manifest no symptoms even after VZV having

becoming latent, some people allow reactivation and propagation of VZV hidden in ganglions due to weakened responses in their immunologic mechanism and, whereby vesicles and neuralgia are manifested in the nerve field invariably unilaterally and zonally.

HZ as a result of this reactivation of VZV occurs in several parts simultaneously mainly on the chest and/or face. Eruption subsides, on an average, in about 3 weeks and neuralgia gradually abates in 1 to 3 months. And, in the aged, intractable neuralgia called PHN may remain or recur, causing troubles in everyday life, such as insomnia. The pain caused by VZV includes acute stage (HZ) pain and PHN, among which PHN, in particular, has been very difficult to treat effectively.

In cases where the pain due to HZ is slight, oral administration of an NSAID (nonsteroidal anti-inflammatory drug) is effective as the case may be, whereas, in the case of severe pain, it is necessary to perform nerve block. In the case of PHN, it is difficult to produce analgesic effects on severe pains in old cases having a history of 1 year or longer even by means of nerve block. Generally, administration of an NSAID is ineffective and, although oral administration of a tricyclic antidepressant or

clonidine, iontophoresis with lidocaine, application of a 0.075% capsaicin ointment, a 2% aspirin ointment or a lidocaine ointment and use of an indomethacine patch and so forth have been attempted, there is almost no effective key therapeutic method available at present.

The local anesthetic effect of lidocaine is well known, and lidocaine has already been used in nerve block or iontophoresis as a treatment to alleviate the pain of HZ and PHN. These methods, however, require patients to receive regular outpatient treatment and often produce some problems, namely its anesthetic effect is unreliable and it causes anxiety about infection upon its injection or about electric shock. Therefore, the establishment of an effective therapeutic method has been desired which enables home treatment, gives no feeling of anxiety to patients and is free of the possibility of infection by frequent injections.

As a method for realizing such desire, a therapeutic method is conceivable which uses a medicinal means, such as an oral administration or an external administration, other than injection or dripping. Generally, however, as frequently reported for oral preparations, there are problems, for example

long-term use may result in manifestation of side effects such as gastrointestinal disorder and the drug has to pass through the liver before arriving at the target site and therefore undergoes partial degradation in the liver (first pass effect). A further known drawback is that even if a side effect should have once been produced after administration, the drug can never be removed.

Therefore, various preparations suited for transdermal administration have been reported as dosage forms capable of removing these drawbacks. As external lidocaine preparations, ointments, jellies, sprays and the like have been marketed but, as far as skin surface anesthesia is concerned, satisfactory anesthetic effects have not been obtained as yet. Further, lidocaine gels as hospital preparations are sometimes used in the treatment of HZ and PHN but an ODT (occlusive dressing technique) is required after application. The development of an effective patch which can be used in a simple and easy manner has thus been desired. No such one has been marketed as yet.

Meanwhile, Japanese Patent Prepublication No. 02-300138 discloses a lidocaine-containing "composition characterized in that a long-term pain-alleviating effect is sustained after removal of

the preparation". However, as can be deduced from the mere description "the effect was evaluated at one-hour intervals following lidocaine application for 4 hours", the preparation is expected only to be effective for about 4 hours at the longest. A preparation which is effective for a longer period of time is demanded.

On the other hand, Japanese Patent Prepublication No. 04-305523 discloses a patch for external use for the treatment of pain due to HZ and of PHN. This external patch is a preparation which comprises a water-soluble polymer, water and a water retaining agent as essential components and contains lidocaine or a salt thereof in the so-called aqueous poultice or cataplasm base. In this reference, moisture is said to be effective for improving the permeability of the drug. Since, in reality, however, lidocaine is scarcely soluble in water, addition of a large amount of lidocaine may result in precipitation of crystals in the water-soluble base, hence the alleged pharmacological effect is questionable. The use of a salt of lidocaine in lieu of lidocaine is also conceivable. While such a lidocaine salt itself is readily soluble in water, it is a substance hardly absorbable through the skin. The preparation disclosed in the reference cited above is thus evaluated

as one that can hardly be said to be satisfactory from the viewpoint of actual drug absorption.

Further, the present inventors have already found out a patch having sustained pain-alleviating action characterized by that lidocaine as an active ingredient and an oleaginous component, as a release controlling agent, selected from the group consisting of liquid paraffins, higher fatty acids and vegetable oils are incorporated in an adhesive mass base comprising a styrene-isoprene-styrene block copolymer and a tackifier and the resulting mixture is supported on a flexible backing (Japanese Patent Prepublication No. 10-147521). The period over which the pain-alleviating effect of this preparation has been confirmed, however, is only 24 hours. A preparation capable of releasing a local anesthetic, such as lidocaine, over a longer period of time is thus demanded.

For obtaining a transdermal preparation having good application characteristics, it is a matter of course that its efficacy and safety should have been confirmed and, in addition, it should have those characteristics which are fundamental to transdermal preparations and typical of patches. Thus, for instance, it should adhere to the skin well, should

not cause abrasion of the stratum corneum upon peeling thereof, and should not give pain upon peeling thereof. In particular, the pain due to the diseases in question lasts long in many cases, hence repeated administrations to the painful site or sites on the skin is anticipated; therefore, it is required that the abrasion of the stratum corneum, which is causative of skin irritation, be slight. Thus, for preparing a practical transdermal preparation, it is necessary to select the adhesion, keying, cohesion and other parameters in a manner such that they are well balanced among them. In the actual circumstances, however, it can hardly be said that a transdermal preparation having fully satisfactory characteristics has so far been provided.

Thus, under the circumstances in which it can hardly be said that a practical patch suited for alleviating lasting pains, such as the pain due to HZ or PHN, is at present available, the development of a transdermal preparation more improved in efficacy, safety and application characteristics is required.

DISCLOSURE OF INVENTION

The present inventors made investigations in an attempt to obtain a transdermal preparation which

contains a local anesthetic, typically lidocaine, as an active ingredient and has high practicability.

Meanwhile, patches, which are transdermal preparations, are roughly classified into two types: poultices derived from an aqueous base comprising a water-soluble polymer, water and a water-retaining agent, among others, and tape preparations derived from an oleaginous (nonaqueous) base whose base is a elastomer selected from among styrene-isoprene-styrene block copolymers, styrene-butadiene- styrene block copolymers, polybutenes, polyisoprenes, butyl rubbers, natural rubbers and the like. As a result of preliminary investigations made by the present inventors, it was found that poultices are relatively low in adhesion and difficult to retain on the affected part for a long period of time, hence are unsuitable for achieving the object of the present invention and, further, that since they contain water, they are, in an aspect, inferior in release and transdermal absorption of the main ingredient lidocaine. It was also found that they have more problems to solve as compared with oleaginous bases; for example, since their properties (which have influences on the drug release and adhesion as well) change as a result of evaporation of water after

application, they are not suited for long-period application. Furthermore, it was judged that, in the case of HZ or PHN in which the pain may be increased by external stimulation, the stimulation resulting from cooling of the affected part is also unfavorable and, therefore, water-free, oleaginous base-derived tape preparations are rather preferred.

However, tape preparations produced by merely incorporating a local anesthetic, such as lidocaine, in an oleaginous base comprising a elastomer such as mentioned above cannot attain sustained percutaenous absorbability or sufficient adhesion. Further contrivances were needed for obtaining a practical transdermal preparation for lasting pains.

Accordingly, the present inventors made intensive investigations for obtaining a nonaqueous system-based transdermal preparation which enables to prolong and sustain the effect of a local anesthetics, such as lidocaine, can be used repeatedly for a long period of time without causing abrasion of the stratum corneum and is suited for the alleviation of HZ pains or PHN and, as a result, they found that the above object can be accomplished when a adhesive mass is prepared by incorporating liquid paraffin as a release controlling agent and butyl rubber in a adhesive mass

base comprising a styrene-isoprene-styrene block copolymer and an alicyclic saturated hydrocarbon resin as a tackifier component, and a local anesthetic, such as lidocaine, is incorporated in this mass, and they have now completed the present invention.

Thus, the present invention provides a tape preparation for transdermal absorption which is characterized by that a adhesive mass prepared by incorporating 1-30 parts by weight of a local anesthetic as an active ingredient in 100 parts by weight of a nonaqueous adhesive mass base comprising 5-50% by weight of a styrene-isoprene-styrene block copolymer, 1-60% by weight of an alicyclic saturated hydrocarbon resin, 5-60% by weight of liquid paraffin and 1-30% by weight of butyl rubber is supported on a backing.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the changes of the lidocaine concentrations in the skin following application of the preparation of Example 2. Fig. 2 shows the local anesthetic effects following application of the preparation of Example 2 and of the preparation of Comparative Example 5.

Fig. 3 shows the changes in plasma lidocaine concentrations for the case in which the preparation

of Example 2 was applied for 24 hours and then peeled off and for the case in which the same preparation was continuously applied for 48 hours. Fig. 4 shows the changes in plasma lidocaine concentrations as found when the preparation of Example 2 or Comparative Example 5 was continuously applied. Fig. 5 shows the amounts of the stratum corneum peeled off upon peeling off the preparation of Example 2 or Comparative Example 5 following application thereof.

BEST MODES FOR CARRYING OUT THE INVENTION

The tape preparation for transdermal absorption of the present invention is produced by preparing a adhesive mass by incorporating a local anesthetic, liquid paraffin and butyl rubber in a nonaqueous adhesive mass base comprising a styrene-isoprene-styrene block copolymer (hereinafter sometimes referred to also as "SIS"), which is a main adhesive component, and an alicyclic saturated hydrocarbon resin, which is a tackifier component, and causing the adhesive mass to be supported on a backing in the conventional manner.

The adhesive mass base component SIS is a component essential for providing adhesion required of a patch. This SIS is already available on the market

as a adhesive mass base material and, in the practice of the present invention, such commercial product can be utilized. This SIS base is incorporated preferably at an amount of 5-50%, more preferably 10-40%, relative to the adhesive mass weight. When it is less than 5%, the cohesion will become reduced, which may cause such a problem as adhesive deposit after the application. When it is in excess of 50%, the mass becomes excessively hard, which may cause insufficient adhesion.

The alicyclic saturated hydrocarbon resin included in the nonaqueous adhesive mass base components is a resin capable of providing adhesion only when combined as a tackifier component with the adhesive base. If this tackifier component is absent, no adhesion can be generated, hence the function as a tape preparation cannot be performed. As examples of the alicyclic saturated hydrocarbon resin which are specifically utilizable, there may be mentioned those available on the market such as Arkon P series and Arkon M series (both being products of Arakawa Chemical Industries). This alicyclic saturated hydrocarbon resin is incorporated preferably at an amount of 1-60%, more preferably 10-50%. When the amount of this resin is smaller than 1%, the adhesion will be lost and peeling tends to occur. When it is in excess of 60%, the

adhesion is so strong that pain may be caused on the occasion of peeling off, or abrasion of the stratum corneum may occur and cause skin irritation.

Further, the liquid paraffin, as an oleaginous component, controls the release of a local anesthetic, such as lidocaine, from the adhesive mass and at the same time softens the adhesive of the adhesive mass. By incorporating this, long-lasting release of the local anesthetic is realized and the tape form preparation is provided with flexible physical properties. Therefore, without using this oleaginous component, it is impossible to obtain an elastic and flexible tape preparation effective against such diseases as HZ and PHN and capable of remaining adhesive and releasing a local anesthetic, such as lidocaine, stably for a long period of time. The liquid paraffin is incorporated preferably at an amount of 5-60%, more preferably 10-40%, relative to the weight of the adhesive mass. When it is less than 5%, the long-term releasability of the local anesthetic, such as lidocaine, and the ability to morphologically follow the skin will become reduced. When it is in excess of 60%, excessive flexibility will result, the cohesion will be lost and adhesive deposit may occur after the application.

Furthermore, the butyl rubber used in the tape preparation for transdermal absorption of the present invention is used to modify the flexibility of the adhesive mass, which is insufficient when the SIS is used alone, to a favorable level and prevent the cohesion of the adhesive mass from being decreased by the liquid paraffin.

By combinational using the above liquid paraffin and butyl rubber, it is intended that the long-lasting release of the local anesthetic, such as lidocaine, from the adhesive mass and an adequate level of adhesion be secured and that the stratum corneum be prevented from being abraded. For this purpose, the butyl rubber to be used in the practice of the present invention preferably has a molecular weight of about 400,000. The butyl rubber is incorporated preferably at an amount of 1-30%, more preferably 5-15% and, by doing so, an adhesive mass having high wettability and good adhesion can be obtained.

As the active ingredient local anesthetic which can be incorporated in the thus-obtained adhesive mass, there may be mentioned lidocaine, procaine, oxyprocaine, dibucaine, tetracaine, bupivacaine, mepivacaine, propitocaine, and salts of these. Such a local anesthetic is incorporated at the adhesive mass

composition preferably at an amount of 1-30% by weight (hereinafter, "%" for short), more preferably 5-20%.

In the above adhesive mass composition, a filler may be incorporated for retaining the thickness of the adhesive mass layer and/or preventing the adhesive mass from becoming excessively soft and flexible and permeating through the backing. As the filler, there may be mentioned, for example, kaolin, titanium oxide, talc, calcium carbonate, silicate salts, silicic acid, aluminum hydrate, barium sulfate, calcium sulfate and the like.

Further, an antioxidant, such as dibutylhydroxytoluene, and/or a perfume, such as peppermint oil, and other additives generally used in ordinary tape preparations may be added, when necessary, to the adhesive mass composition of the present invention.

The tape preparation for transdermal absorption of the present invention is prepared in the form of tape preparations by preparing an adhesive mass composition by mixing and dissolving the above essential components and then causing the composition to be supported on a flexible backing, as mentioned above. An example is now shown. First, an SIS and a butyl rubber base, liquid paraffin and an alicyclic

saturated hydrocarbon resin, together with a filler and/or an optional ingredient or ingredients to be added where necessary, are melted and mixed up under the heat, and a local anesthetic is added thereto, followed by mixing for sufficient dissolution.

Then, this adhesive mass is casted over a flexible backing and cooled and then, if necessary, a release liner is applied, followed by cutting to an adequate surface area, whereby a tape preparation can be prepared.

The backing to be used here is preferably a flexible film- or sheet-like material so that the tape preparation for transdermal absorption can be provided with the ability to follow the movement of the skin when it is applied as a tape preparation, for instance, to such movable site. As suitable materials, there may be mentioned, for example, nonwoven fabrics, vinyl chloride films, knitted fabrics, cotton cloths, polyurethane films and the like. Among them, nonwoven fabrics and knitted fabrics are preferred. The thickness of the adhesive mass formed on the backing is preferably 50-500 μm, more preferably 100-300 μm.

As preferred embodiments of the thus-obtainable tape preparation for transdermal absorption of the

present invention, there may be mentioned, for example, tape preparations produced by forming, on a nonwoven fabric (backing), a 100-300 μm thick layer of an adhesive mass with a lidocaine content of 5-20%, a styrene-isoprene-styrene block copolymer content of 10-40%, a liquid paraffin (oleaginous component) content of 10-40%, a butyl rubber content of 5-15% and an alicyclic saturated hydrocarbon resin (tackifier component) content of 20-50%.

The tape preparation for transdermal absorption of the present invention as explained hereinabove is highly effective not only against such diseases as HZ and PHN but also against pains on the occasion of high frequency therapy or laser therapy, pains in the treatment of liver spots or dark red birthmarks or on the occasion of biopsy, and pains at the time of skin grafting for the treatment of thermal burns or pains in the treatment of molluscum contagiosum. In addition to the above, it will be usable also against postoperative pains and pains on the occasion of dental treatment, and so forth.

The transdermal administration of a local anesthetic utilizing the tape preparation for transdermal absorption of the present invention is made either for the purpose of alleviating pains upon

venipuncture or the like or for the purpose of alleviating pains caused by HZ or PHN. However, there is a great difference between both concepts of pain alleviating.

Thus, in the former case, an instantaneous action is first of all required of the preparation and it is only required that the pain- alleviating effect be produced on the occasion of such treatment as venipuncture. In the latter case, on the contrary, the maintenance of effect, namely how long pains can be alleviated, is required rather than the immediate action. For meeting such requirement, from the viewpoint not only of efficacy but also of adhesion, long-period efficacy maintenance and long-period fixation on the affected part are required in the latter case while, in the former case, only about 1 hour of maintenance of such is sufficient. The period over which the effect lasts should preferably be as long as possible and the frequency of tape preparation exchange should preferably be as low as possible. For the symptom called allodynia in which mere contacting, for instance, evokes pain, such conditions are particularly favorable to the patients concerned.

The tape preparation for transdermal absorption of the present invention is characterized by that it is excellent not only in long-lasting pain-alleviating

effect but also in adhesion to and ability to morphologically follow the site of application and, furthermore, the preparation is also effective for preventing the stratum corneum from being abraded. Therefore, it can be said to be a preparation very suited for the purpose of alleviating pains caused by HZ or PHN.

Although adhesive masses can also be obtained using other substances such as natural rubbers and acrylic rubbers as main adhesive components of tape preparations for transdermal absorption, it was found, as a result of investigations concerning the releasability of local anesthetics such as lidocaine, that SISs are most preferred. However, SISs alone are insufficient to provide the adhesive masses with flexibility. In attempts to modify them by conventional techniques, a phenomenon was observed that SISs, which have a molecular weight of only about 200,000, allowed the adhesive masses to penetrate through the backing, resulting in decreases in adhesion. For preventing this phenomenon, a butyl rubber with a high molecular weight, namely a molecular weight of not less than 400,000, is incorporated to thereby improve the physical properties of the adhesive mass base.

The incorporation of this butyl rubber was further found to be effective for suppressing the decrease in adhesive mass cohesion which otherwise results from the incorporation of liquid paraffin as a release controlling agent.

On the contrary, Japanese Patent Prepublication No. 02-300138 discloses examples in which a salicylate ester, such as methyl salicylate or glycol salicylate, is used as a solvent, namely as means of dissolving lidocaine in adhesive masses. When attempts were made to use such esters in the preparation of the present invention, the esters separated from adhesive masses, causing insufficient adhesion and failing to give the form of required preparations, hence they could not be used successfully.

As mentioned above, as a result of incorporation of butyl rubber in SIS, the tape preparation for transdermal absorption of the present invention has established a balance between the flexibility of the adhesive mass and the cohesion of the adhesive mass as well as the sustained release of local anesthetics and its safety in long-period application to the skin.

The following examples, comparative examples and test examples explain the present invention but those examples are by no means limitative of the scope

thereof. In the examples or comparative examples, "part(s)" means "part(s) by weight" unless otherwise specified.

Example 1

A tape preparation for transdermal absorption was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	5 parts
Styrene-isoprene-styrene block copolymer*	22 parts
Butyl rubber**	5 parts
Alicyclic saturated hydrocarbon resin***	33 parts
Liquid paraffin	30 parts
Titanium oxide	5 parts
Antioxidant	0.1 part

* Kraton D-1107 (product of Shell Chemical)

** Exxon Butyl -065 (product of Exxon Chemical)

*** Arkon P-100 (product of Arakawa Chemical Ind.)

(Production method)

The styrene-isoprene-styrene block copolymer and the other components were melted under the heat and then lidocaine was added, followed by stirring. The mass obtained was then casted over a nonwoven fabric and allowed to cool. A polyethylene terephthalate

film was applied thereto, followed by cutting to an adequate size to give a tape preparation containing 1.07 mg/cm^2 of lidocaine.

Example 2

A tape preparation for transdermal absorption was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	10 parts
Styrene-isoprene-styrene block copolymer*	25 parts
Butyl rubber**	5 parts
Alicyclic saturated hydrocarbon resin***	31 parts
Liquid paraffin	24 parts
Zinc oxide	5 parts
Antioxidant	0.1 part

* Kraton D-1107 (product of Shell Chemical)

** Exxon Butyl -065 (product of Exxon Chemical)

*** Arkon P-100 (product of Arakawa Chemical Ind.)

(Production method)

A tape preparation containing 2.14 mg/cm^2 of lidocaine was obtained in the same manner as in Example 1.

Example 3

A tape preparation for transdermal absorption was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	20 parts
Styrene-isoprene-styrene block copolymer*	26 parts
Butyl rubber**	5 parts
Alicyclic saturated hydrocarbon resin***	30 parts
Liquid paraffin	14 parts
Titanium oxide	5 parts
Antioxidant	0.1 part

* Kraton D-1111 (product of Shell Chemical)

** Exxon Butyl-065 (product of Exxon Chemical)

*** Arkon M-100 (product of Arakawa Chemical Ind.)

(Production method)

A tape preparation containing 4.28 mg/cm^2 of lidocaine was obtained in the same manner as in Example 1.

Comparative Example 1

A tape preparation for transdermal absorption was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	10 parts

Styrene-isoprene-styrene block copolymer*	34 parts
Butyl rubber**	7 parts
Alicyclic saturated hydrocarbon resin***	42 parts
Zinc oxide	7 parts
Antioxidant	0.1 part

* Kraton D-1112 (product of Shell Chemical)

** Exxon Butyl -065 (product of Exxon Chemical)

*** Arkon P-90 (product of Arakawa Chemical Ind.)

(Production method)

The styrene-isoprene-styrene block copolymer and butyl rubber and the other components were melted under the heat and then lidocaine was added, followed by stirring. The mass obtained was then casted over a nonwoven fabric and allowed to cool. A polyethylene terephthalate film was applied thereto, followed by cutting to an adequate size to give a tape preparation containing 2.14 mg/cm^2 of lidocaine.

Comparative Example 2

A tape preparation for transdermal absorption was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	10 parts
Styrene-isoprene-styrene block copolymer*	25 parts

Butyl rubber**	29 parts
Alicyclic saturated hydrocarbon resin***	31 parts
Zinc oxide	5 parts
Antioxidant	0.1 part

* Kraton D-1107 (product of Shell Chemical)

** Exxon Butyl -065 (product of Exxon Chemical)

*** Arkon P-100 (product of Arakawa Chemical Ind.)

(Production method)

A tape preparation containing 2.14 mg/cm^2 of lidocaine was obtained in the same manner as in Comparative Example 1.

Comparative Example 3

A gel preparation was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	10 parts
Polysorbate 20	12 parts
Carbomer 940	0.9 part
Diisopropanolamine	0.8 part
Propylene glycol	76.3 parts

(Production method)

A gel-like preparation was prepared by thoroughly mixing up the above components until uniformity was attained.

Comparative Example 4

A poultice preparation was prepared according to the formulation and production method shown below.

(Formulation)

Lidocaine	5 parts
D-Sorbitol	10 parts
Glycerol	20 parts
Propylene glycol	10 parts
Sodium polyacrylate	4 parts
Carboxymethylcellulose sodium	5 parts
Polyacrylic acid	3 parts
Methyl para-hydroxybenzoate	0.1 part
Propyl para-hydroxybenzoate	0.05 part
Aluminum hydroxide	0.3 part
Purified water	balance
Total amount	100 parts

(Production method)

To purified water were added D-sorbitol and polyacrylic acid, followed by mixing up. Thereto was further added a solution of lidocaine in propylene glycol, followed by mixing up. To this mixture was added a dispersion of sodium polyacrylate, carboxymethylcellulose sodium, aluminum hydroxide, methyl para-hydroxybenzoate and propyl

para-hydroxybenzoate in glycerol, followed by thorough mixing to give a uniform mixture. The thus-obtained adhesive mass was casted over a nonwoven fabric, and a polyethylene terephthalate film was applied thereto, followed by cutting to an adequate size to give a poultice preparation containing 5 mg/cm^2 of lidocaine.

Comparative Example 5

In an inert gas atmosphere, a flask was charged with 93 parts of octyl acrylate and 7 parts of acrylic acid, 0.1 part of benzoyl peroxide was added as a polymerization initiator, and polymerization was effected in ethyl acetate while maintaining the temperature at 60℃, to give an acrylic pressure-sensitive adhesive solution (solution A) (solid content 38.9%).

To 40 parts of the solid matter in this solution was added 60 parts of lidocaine, followed by addition of ethyl acetate to give a solution with a solid content of 35%. A polyetser release liner was coated with the above solution to a thickness after drying of 20 μm, and the coating was dried at 100℃ for 5 minutes to give a pressure sensitive adhesive layer with a lidocaine content of 60%. The thus-obtained

lidocaine-containing pressure sensitive adhesive layer was overlaid with a 12-μm-thick backing made of a polyester, the assembly was allowed to stand at room temperature for 24 hours to allow the lidocaine in the pressure sensitive adhesive layer to crystallize, to give a tape form preparation.

Test Example 1

Applicability test:

The tape preparations and poultice preparation (cut to a size of 10 cm $\times$ 7 cm) obtained in Examples 1-3 and Comparative Examples 1, 2, 4 and 5 were each applied to the lateral region of the chest (where HZ is found frequently), which is a region showing relatively great movements, of each healthy human adult. At 12 hours, 24 hours and 48 hours after application, the preparations were observed for their conditions of adhesion. The results are shown in Table 1 (n = 20).

Table 1

	Number of persons (out of 20) showing the conditions of adhesion defined below								
	After 12 hours			After 24 hours			After 48 hours		
	No turn up	Slight turn up	Dropping	No turn up	Slight turn up	Dropping	No turn up	Slight turn up	Dropping
Exam.1	20	0	0	20	0	0	20	0	0
Exam.2	20	0	0	20	0	0	20	0	0
Exam.3	20	0	0	20	0	0	20	0	0
Comp.1	0	10	10	0	5	15	0	0	20
Comp.2	0	5	15	0	0	20	0	0	20
Comp.4	0	10	10	0	3	17	0	0	20
Comp.5	0	15	5	0	5	15	0	0	20

As is obvious from Table 1, the preparations of Examples 1-3 remained satisfactorily adhering to the skin after 48 hours and scarcely showed skin irritation. The preparations of Comparative Examples 1, 2, 4 and 5 were somewhat inferior in adhesion and showed a certain extent of skin irritation.

Test Example 2

Pharmacokinetic test:

Intradermal pharmacokinetics of lidocaine were studied in guinea pigs.

The lateral abdominal region of each guinea pig was cut off by means of hair clippers and a shaver, cleanly wiped with water-moistened absorbent cotton and, after removal of moisture, the preparation obtained in Example 2 was administered. A protective

tape was applied to the site of administration for fixation of the preparation.

(Results)

The results of the intradermal pharmacokinetic behavior study of lidocaine are shown in Fig. 1. As is obvious from Fig. 1, the intradermal concentration of lidocaine rapidly increased after application and remained at high levels until 48 hours later.

Test Example 3

Local anesthetizing test in humans:

The tape preparations of Example 2 and Comparative Example 5 were tested for their anesthetic effect in humans.

The tape preparation or transdermal preparation cut to a diameter of 23 mm was applied to the inside of the upper arm of each human subject and, after peeling off, three points in the application site were pricked with a mandolin string (25G × 70mm needle) and the level of pain was compared with that felt at an unapplied site.

(Results)

The results are shown in Fig. 2 (n = 5). With the preparation of Example 2, the anesthetic effect on the level of benumbedness continued until hour 54

and the painless level, which falls within the actual therapeutic range, lasted even after hour 24 and lasted until hour 72. On the other hand, with the preparation of Comparative Example 5, the effect lasted only for at most 24 hours. This fact indicated that the long-acting tape preparation for transdermal absorption of the present invention is very useful from the viewpoint of avoiding those side effects indigenous to tape preparations, such as abrasion of the stratum corneum of the skin, sore and flare, which are anticipated if the duration of effect is short and repeated application is required.

Test Example 4

Measurement of the blood concentration:

For confirming the pharmacokinetics in blood after peeling off, a single application test was conducted in guinea pigs using the tape preparation of Example 2. The preparation was peeled off after 24 hours following application and the blood concentration were examined until 24 hours after peeling off. At the same time, the data were compared with those obtained in the case of application for 48 hours.

(Results)

The results are shown in Fig. 3. After peeling off the preparation, the plasma concentration rapidly disappeared and it was confirmed that the plasma concentration can be maintained for 48 hours if the application is continued. This means that if a side effect should be produced, the blood concentration can be immediately and preferably reduced by peeling off the preparation, unlike injections or oral administration, as mentioned hereinabove.

Test Example 5

Continued application test:

Using the tape preparation of Example 2 of the present invention and the tape preparation prepared in Comparative Example 5, 4-day continuous application was conducted while making reapplication once a day at 24-hour intervals, and blood lidocaine concentration were measured. The preparation of Comparative Example was reapplied once or twice a day and, in the group receiving two reapplications per day, reapplication was performed after 10 hours and 24 hours following the preceding application. The reapplication was made at the same site for 4 days.

(Results)

The results are shown in Fig. 4. In the

continuous application test, the difference in pharmacokinetics as resulting from reapplication of the tape preparations was confirmed. While the blood lidocaine concentration rapidly increased after reapplication of the preparation of Comparative Example 5, an almost constant blood concentration was maintained with the preparation of Example 2. Since the skin stratum corneum is involved in the transdermal absorbability of lidocaine, there is the possibility of a rapid increase in blood concentration when such a preparation is applied to the skin whose stratum corneum shows reduced barrier functions due to repeated application, for instance, hence there is a safety problem. In this respect, it was shown that the influence of the preparation of Example 2 on the stratum corneum is more limited than that of the preparation of Comparative Example 5 and it was thus found that the preparation of the present invention is superior in safety.

Test Example 6

Stratum corneum abrasion test:

The tape preparation of Example 2 of the present invention and the tape preparation prepared in Comparative Example 5 were examined for the ability

to abrade the stratum corneum. Thus, each tape preparation was applied to the upper arm of each respective normal healthy subject and peeled it off 3 hours after the application.

Each preparation removed was transcribed onto a measurement tape and, after washing with ethanol for defatting, the stratum corneum was stained with a staining solution, followed by immersion in an aqueous solution of sodium dodecyl sulfate.

The amount of the eluted staining substance was measured based on the absorbance data. Since the absorbance is proportional to the amount of stratum corneum adhering to the preparation removed, the absorbance was regarded as the amount of stratum corneum abraded.

(Results)

The results are shown in Fig. 5. As is evident from this figure, it was found that the amount of abraded stratum corneum with the tape preparation of Example 2 was smaller than that of the tape preparation of Comparative Example 5. Thus, it was shown that the tape preparation of the present invention is less in the ability to cause stratum corneum abrasion, which is causative of skin irritation, hence is superior in skin safety.

Comparative Example 7

Clinical trial against HZ and PHN:

The tape preparation for transdermal absorption of the present invention in which lidocaine was used as the local anesthetic was applied to 11 patients complaining of pain due to HZ or PHN twice a day (one sheet per application) for 3-7 days and the pain-alleviating effect was examined.

(Results)

The results are shown below in Table 2. It was revealed that the tape preparation for transdermal absorption of the present invention is a drug useful for alleviating pains in peripheral neuralgia.

Table 2

Efficacy	Global rating of improvement	
	Number of subjects	Percentage (%)
Excellent	3	27.3
Good	6	54.5
Fair	1	9.1
Poor	1	9.1
Total	11	100
Excellent + good	9	81.8

Test Example 8

Pain-alleviating test on the occasion of high frequency therapy:

A pain alleviating test was performed using 5

patients treated for liver spot removal as panelists.

Thus, the tape preparation for transdermal absorption of the present invention in which lidocaine was used as the local anesthetic was applied to the treatment site of each patient 1 hour before liver spot removal by means of a high frequency therapy. Just before treatment, the tape preparation was peeled off and liver spot removal was effected by means of a high frequency therapy. The liver spots could be treated without any pain felt by the patient.

INDUSTRIAL APPLICABILITY

The tape preparation for transdermal absorption of the present invention can quantitatively and efficiently release lidocaine and therefore is excellent in duration of effect. It causes stratum corneum abrasion only to be a lesser extent, hence does not decrease the barrier function of the stratum corneum upon continuous application. Therefore, it is a preparation very suited for the purpose of pain alleviation in HZ or PHN and high in safety.

In addition to the above objects, it has a good pain alleviating effect against pains resulting from high frequency therapy or laser therapy, pains upon treatment of liver spots or dark red birthmarks, pains

on the occasion of biopsy, and pains upon skin grafting for the treatment of thermal burns or of molluscum contagiosum, hence has high utility value.

CLAIMS

1. A tape preparation for transdermal absorption which is characterized by that an adhesive mass prepared by incorporating 1-30 parts by weight of a local anesthetic as an active ingredient in 100 parts by weight of a nonaqueous adhesive mass base comprising 5-50% by weight of a styrene-isoprene-styrene block copolymer, 1-60% by weight of an alicyclic saturated hydrocarbon resin, 5-60% by weight of liquid paraffin and 1-30% by weight of butyl rubber is supported on a backing.

2. A tape preparation for transdermal absorption as claimed in Claim 1, wherein the effect of the local anesthetic lasts for 24 to 72 hours.

3. A tape preparation for transdermal absorption as claimed in Claim 1 or 2 which causes stratum corneum abrasion only to be a slight extent even when applied continuously for a long period of time.

4. A tape preparation for transdermal absorption as claimed in any of Claims 1 to 3 which is excellent in duration of effect on alleviating pains due to herpes

zoster or postherpetic neuralgia.

5. A tape preparation for transdermal absorption as claimed in any of Claims 1 to 3 which is excellent in duration of effect on alleviating pains on the occasion of high frequency therapy or laser therapy, pains upon treatment of liver spots or dark red birthmarks, pains upon biopsy, pains on the occasion of skin grafting for the treatment of thermal burns, or pains on the occasion of treatment of molluscum contagiosum.

6. A tape preparation for transdermal absorption as claimed in any of Claims 1 to 5, wherein the local anesthetic is selected from the group consisting of lidocaine, procaine, oxyprocaine, dibucaine, tetracaine, bupivacaine, mepivacaine, propitocaine, and salts thereof.

7. A tape preparation for transdermal absorption as claimed in any of Claims 1 to 5, wherein the local anesthetic is lidocaine.

8. A nonaqueous adhesive mass base which comprises 5-50% by weight of a styrene-isoprene-styrene block copolymer, 1-60% by weight of an alicyclic saturated

hydrocarbon resin, 5-60% by weight of liquid paraffin and 1-30% by weight of butyl rubber.

9. A nonaqueous adhesive mass base as claimed in Claim 8 which causes stratum corneum abrasion only to be a slight extent even when applied continuously for a long period of time.

ABSTRACT

A preparation for transdermal absorption is disclosed which is suited for alleviating lasting pains caused by herpes zoster or postherpetic neuralgia and is practical and more improved in drug efficacy, safety and application characteristics. This tape preparation for transdermal absorption is obtained by causing an adhesive mass prepared by incorporating 1-30 parts by weight of a local anesthetic as an active ingredient in 100 parts by weight of a nonaqueous adhesive mass base comprising 5-50% by weight of a styrene-isoprene-styrene block copolymer, 1-60% by weight of an alicyclic saturated hydrocarbon resin, 5-60% by weight of liquid paraffin and 1-30% by weight of butyl rubber to be supported on a backing.

FIG.1

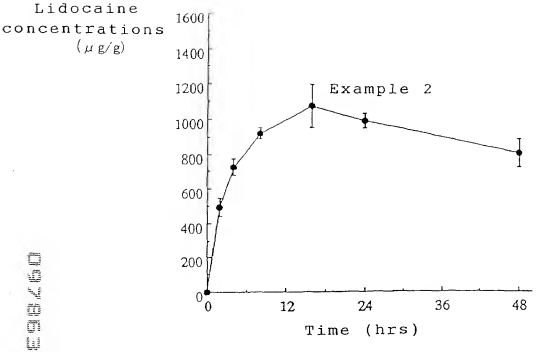

Lidocaine concentrations (μg/g)
1600
1400
1200
1000
800
600
400
200
0
Example 2
0
12
24
36
48
Time (hrs)

FIG.2

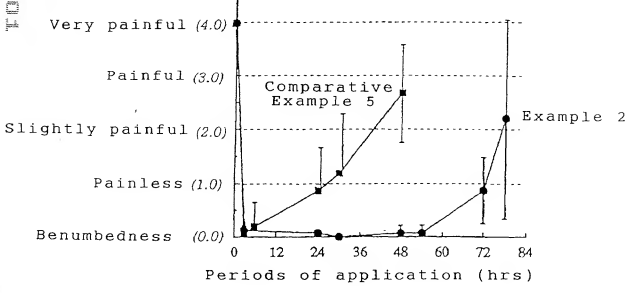

Very painful (4.0)
Painful (3.0)
Slightly painful (2.0)
Painless (1.0)
Benumbedness (0.0)
Comparative Example 5
Example 2
0
12
24
36
48
60
72
84
Periods of application (hrs)

FIG.3

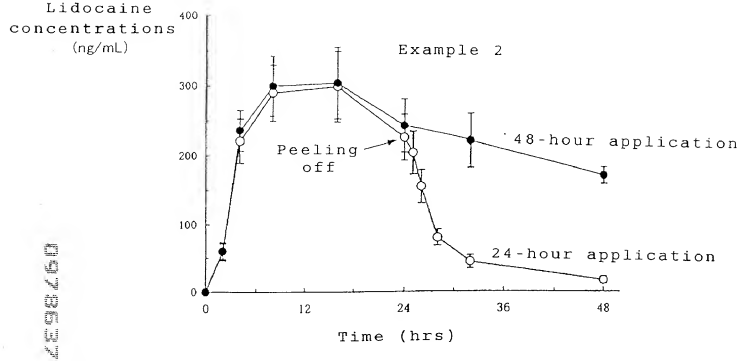

Lidocaine concentrations (ng/mL)
Example 2
Peeling off
48-hour application
24-hour application
400
300
200
100
0
0
12
24
36
48
Time (hrs)

FIG.4

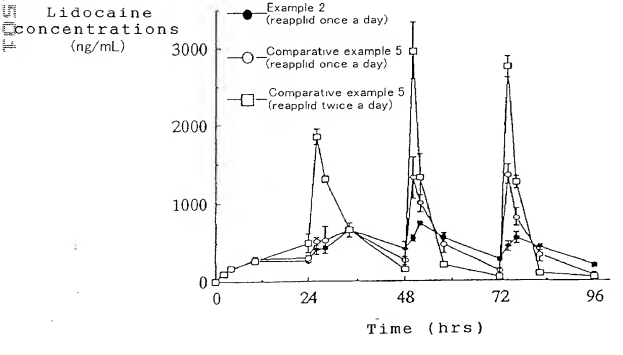
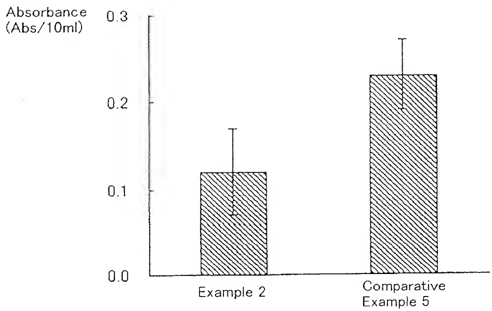

Lidocaine concentrations (ng/mL)
Example 2 (reapplid once a day)
Comparative example 5 (reapplid once a day)
Comparative example 5 (reapplid twice a day)
3000
2000
1000
0
0
24
48
72
96
Time (hrs)

FIG.5



Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

As a below named inventor, I hereby declare that:

私の住所、私書箱、国籍は下記の私の氏名の後に記載された通りです。

My residence, post office address and citizenship are as stated next to my name.

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

TAPE MATERIAL FOR TRANSCUTANEOUS ABSORPTION

上記発明の明細書は、

- ☐ 本書に添付されています。
- ☒ ___月___日に提出され、米国出願番号または特許協定条約国際出願番号を_____とし、
  （該当する場合）_____に訂正されました。

the specification of which

- ☐ is attached hereto.
- ☒ was filed on September 9, 1999
  as United States Application Number or
  PCT International Application Number
  PCT/JP99/04905 and was amended on
  _____ (if applicable).

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

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Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	Priority Claimed 優先権主張	
282197/1998	Japan	☒ Yes はい	☐ No いいえ
		☐ Yes はい	☐ No いいえ

(Day/Month/Year Filed) (出願年月日)
5/October/1998

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☐ I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)

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☐ I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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(弁護士、または代理人の指名及び登録番号を明記のこと)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

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(第三以降の共同発明者についても同様に記載し、署名すること)

(Supply similar information and signature for third and subsequent joint inventors.)

Japanese Language Declaration
（日本語宣言書）

3-02

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（第六またはそれ以降の共同発明者に対しても同様な情報および署名を提供すること。）

(Supply similar information and signature for third and subsequent joint inventors.)